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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/530,893
Filing Date: February 27, 2006
Appellant(s): PLOUET ET AL.

Robert E. Goozner
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 05/18/2010appealing from the Office action mailed 12/30/2009.

(1) Real party in interest(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:
Claim 36 is pending and rejected in this application.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except

for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

Saito et al., "Production of monoclonal antibodies reactive with tumor vasculature by immunization of mice with angiogenic factor-induec human umbilical vein endothelial cells". Proceedings of the American Association for Cancer Research Annual Meeting, March 2002, Vol. 43, pp 257, Abstract # 1278.

Concina et al., "The mitogenic effect of 17beta-estradiol on in vitro endothelial cell proliferation and on in vivo reendothelialization are both dependent on vascular endothelial growth factor." J Vasc Res. 2000;37(3):202-208.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Saito et al. (Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 257)) in view of Concina et al (J Vasc Res. 2000 May-Jun;37(3):202-8).

Saito et al teach a method for the production of monoclonal antibodies reactive with tumor vasculature by immunization of mice with angiogenic factor-induced human umbilical vein endothelial cells (see title in particular). Saito et al teach that the development of new vessels, a

phenomenon called angiogenesis, is essential for the development and progression of cancer and consequently, inhibition of angiogenesis may be an effective strategy for the treatment of cancer. Targeting of tumor vasculature using monoclonal antibodies (Mabs) may be an effective approach to inhibit angiogenesis, and for this purpose, the development of monoclonal antibodies reactive specifically with tumor vascular endothelial cells is necessary. One of the most important restrictions for the clinical application of these antibodies is the reactivity with normal vasculature as well as with other normal cells. In an attempt to produce Mabs specific for angiogenic endothelium, we immunized mice with human umbilical vein endothelial cells (HUVECs) stimulated with angiogenic factors, namely vascular-endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and EEP, a growth factor obtained from new-born bovine brains added with murine epidermal growth factor and heparin. With this approach, we obtained several monoclonal antibodies reactive with HUVECs. Among them, some were confirmed to be specifically reactive with tumor vasculature, by immunohistochemistry of frozen-sections of colon cancer and normal colonic mucosa. Neither endothelium of normal colonic mucosa nor the normal blood cells reacted with these Mabs (see abstract).

Saito et al reference teachings differ from the claimed invention only in the recitation that the angiogenic phenotype being obtained by culturing endothelial cells removed from an aorta in a medium containing a supplement consisting essentially of oestradiol and VEGF in claim 36.

However, Concina et al teaches the mitogenic effect of 17B-Estradiol (E2, i.e. claimed oestradiol) on *in vitro* endothelial cell proliferation and on *in vivo* reendothelialization are both dependent on vascular endothelial growth factor (VEGF) (see title). Concina et al teach that local delivery of VEGF accelerates the reendothelialization occurring after arterial injury and attenuates intimal hyperplasia in balloon-injured rat carotid artery. Similarly, a pharmacological dose of E2 was recently reported to promote reendothelialization in castrated female rats (see page 203, 1st col., 1st full ¶). Concina et al provide a study to determine the mechanism by which E2 promotes endothelial cell proliferation. Concina et al teach uses foetal bovine aortic endothelia cells (FBAEC) to study the action of estradiol. Concina et al teach that thoracic aorta VEGF content was increased in E-2-treated rats compared to control rats (see abstract and Fig.

3). Concina et al teach VEGF quantification in the conditioned media of FBAEC revealed that E2 was able to induce VEGF synthesis in a dose-dependent fashion (see page 204, 2nd col., last sentence, and Fig. 3). Fig. 3 shows the effect of E2 on VEGF content in conditioned medium of FBAEC, wherein FBAEC were incubated with E2 for 48hrs. Concina et al teach that VEGF is involved in increased reendothelialization elicited by E2 in vivo and demonstrate that E2 increases the VEGF content in the thoracic aorta, and that the blocking of endogenous VEGF with an anti-VEGF antibody abolishes the effect of E2 on both reendothelialization and intimal hyperplasia inhibition. Also, the anti-VEGF antibody abolishes the E2-elicited proliferation of FBAEC (see page 207, last ¶). Concina et al teach that it cannot be excluded that E2 might act on the recently described endothelial cell progenitors which express VEGFR2 and become incorporated into sites of active angiogenesis. The enhancement of endothelium-derived nitric oxide bioactivity by E2 could contribute to potentiate the VEGF-dependent proliferation of the macrovascular endothelium (see page 207, 2nd col., last ¶). Finally, Concina et al teach that endothelial cells in particular appear to be a target for estradiol 17β (E2) because endothelial cells express the estrogen receptor (see page 202, under Introduction).

It would have been obvious to one skilled in the art at the time the invention was made to immunize the E2-treated FBAEC which induce VEGF synthesis taught by Concina et al in a method of producing monoclonal antibodies reactive with tumor vasculature taught by Saito et al. Given that local delivery of VEGF accelerates the reendothelialization and a pharmacological dose of E2 also promotes reendothelialization, it would have been obvious to one skilled in the art at the time the invention was made to exogenously supplement the medium with oestradiol and VEGF to induce cell proliferation and reendothelialization. It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; the idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Those of skill in the art would have had reason to use the FBAEC taught by Concina et al as a substitute for the immunization of mice taught in Saito et al because, like the HUEVC taught in

Saito et al, FBAEC cells treated with Oestradiol and VEGF have angiogenic phenotype. Substituting a known element for another, to yield the known result, is obvious. *See KSR*, 550 U.S. at 416, 421.

It has been held that "[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, Id at 416 (2007).

"When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." Id at 421.

While the prior art teachings may be silent as to the specific angiogenic phenotype recited in the claim; the method, the aortic endothelial cells and the culturing conditions (oestradiol and VEGF) used in the reference method are the same as the claimed method. Therefore the claimed angiogenic phenotype is considered inherent properties.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

7.1 Sole Ground - SAITO et al. in view of CONCINA et al.

On page 5 of the brief under section 7.1, Appellant submits that SAITO et al. use Human Umbilical Vein Endothelial Cells (HUVEC) that are stimulated in vitro with proangiogenic factors, i.e., basic Fibroblast Growth Factor (bFGF), Vascular Endothelial Growth Factor

(VEGF), and EEP, a growth factor obtained from new-born bovine brains added with murine Epidermal Growth Factor (EGF) and heparin. The cell treatment 'activates" HUVEC cells, and they acquire an angiogenic phenotype. Appellant submits that SAITO et al. use a combination of growth factors that differs from the combination used in the present invention, i.e., oestradiol and VEGF only. Appellant submits that CONCINA et al. disclose that 17β-Esteradial (E2) (hereafter referred to as oestradiol) has mitogenic effects on in vitro endothelial cells derived from Fetal Bovine Aortic Endothelial Cells (FBAEC). This accounts for the stimulation of VEGF which will be secreted and will act in an autocrine way on the cell which has produced it. In a nutshell, CONCINA et al. describe exogenous oestradiol and endogenous VEGF whereas in the invention the cells are treated with exogenous oestradiol and exogenous VEGF. On the bottom of page 6 of the brief, Appellant argues that the combination of the teachings of SAITO et al. in view of CONCINA et al. teach away, since the combination of the teachings of these two documents would lead the skilled artisan in direction divergent from the path that was taken by the applicant (see *In re Gurley*, 27 F.3d 551, 31 U.S.P.Q.2d i130 (Fed. Cir. 1994.) This position is supported by the publications previously provided as evidence, which are attached to this paper and are discussed below. The Office argues that HUVEC and FBAEC treated with angiogenic factors have to be considered both as endothelial cells with angiogenic phenotype.

Appellant submits that at the filing date of the present application, the skilled person would know that many endothelial cells derived from veins, arteries, or arterioles can be used to provide, after stimulation with angiogenic phenotype, endothelial cells with an angiogenic phenotype.

Appellant concluded that the posited document combination can be extended to other endothelial cells derived from veins, arteries, arterioles, placenta, capillary, retina, etc. Appellant contends that at the time the invention was made, the skilled person knew that endothelial cells used as model for studying in vitro angiogenesis are, for example, those set forth in Table 1 of VAILHE et al. (reproduced below), Laboratory Investigation, 2001, Vol. 81, No. 4, pp: 439-452, attached.

Table 1. In Vitro Models of Angiogenesis and Vasculogenesis*

Cells	Mean time required for the formation of CLS	Induction of morphogenesis†	Matrix	Spatial organization	Reference
BCEC, RCEC	3–6 wk	Tumor-cell conditioned medium	Gelatin	2-D	Folkman and Haudenschild, 1980
HUVEC	4–8 wk	S/C‡	+/– Fibronectin, culture dish	2-D	Maciag et al, 1982
RAEx	1 wk	S	Clotted chick plasma	3-D	Nicosia et al, 1982
BAEC (Fetal and calf)	3 d–2 wk	S	Culture dish	2-D	Feder et al, 1983
RCEC	5 d	S	Amniotic membrane (basement surface)	2-D	Madri and Williams, 1983
RCEC	4 d	S	Type IV and V collagen (adsorbed)	2-D	Madri and Williams, 1983
BAEC	3–10 d	S	Type I collagen gel	3-D	Ilsley et al, 1983
BCEC	2–3 d	S	Cells sandwiched in Type I collagen gel	3-D	Montesano et al, 1983
FSC	10 d	S, CEB formation	Culture dish	3-D	Doetschman et al, 1985
MTP, ATF	3–12 d	S	Fibrin, Type I collagen gel	3-D	Montesano et al, 1985
BAEC, ACEC, HUVEC	1 d	S	Fibrin	2-D	Donder et al, 1985
BCEC	5–15 d	C	Type I collagen gel	3-D	Montesano et al, 1986
BCEC	2–3 d	Phorbol ester	Fibrin	3-D	Montesano et al, 1987
HUVEC, HDMEC	1 d	S	Matrigel	2-D	Roberts et al, 1986
BCEC	1–2 d	S/C‡	Fibronectin, collagen IV, Gelatin	2-D	Ingber and Folkman, 1989b
RAEx	1 wk	S‡	Fibrin and Type I collagen gel	3-D	Nicosia and Ottinetti, 1990a and b
BAEC	10–15 d	S	Type I collagen gel	2-D	Vernon et al, 1990
HUVEC	1 d	S	Cells sandwiched in fibrin I or II‡	3-D	Chalupowicz et al, 1995
RFMF	4–6 d	S	Type I collagen gel	3-D	Hoying et al, 1996
CPAEC	2–7 d	S/C‡	Microcarriers embedded in fibrin	3-D	Nehls and Herrmann, 1996a and b
HUVEC, BREC	1–2 d	S	Fibrin	2-D	Vailhé et al, 1996
ESC	11 d	S, EB formation	Semisolid methylcellulose	3-D	Vittet et al, 1996
HPSV	7–21 d	S	Fibrin	3-D	Brown et al, 1996
MMFP	2 wk	S/C‡	Collagen gel	3-D	Arthur et al, 1998
BAEC	3–5 d	S/C‡	Collagen gel	3-D	Vernon and Sage, 1999
BAEC, HUVEC	3 d	S	Type I collagen, fibrin	3-D	Korff and Augustin, 1998
HMMEC	21–50 d	S/C‡	Type I collagen/fibronectin	2-D	Pedatiz et al, 2000

ACEC, adrenal capillary endothelial cells; ATF, adipose tissue fragments; BREC, bovine aortic endothelial cells; BCEC, bovine capillary endothelial cells; BREC, bovine retinal endothelial cells; CEB, bead-stalk-containing cystic embryoid bodies; CPAEC, calf pulmonary aortic endothelial cells; EB, embryoid bodies; ESC, embryonic stem cells; HBMEC, human capillary endothelial cells; HDMEC, human dermal microvascular endothelial cells; HMMEC, human mammary microvascular endothelial cells; HPSV, human placental blood vessels; HSMEC, human umbilical vein endothelial cells; MMFP, mice mammospheric fat pad; MTP, mammalian tissue fragments; RAEx, rat aortic explants; RCEC, rat capillary endothelial cells; RFMF, rat fat microvascular fragments; SLS, capillary-like structures; S, cytokines; S, spontaneous.

*Adapted from Ingber and Folkman, 1988, with permission.

†See references for accurate details.

‡Fibrin I (pink), fibrin, which lacks fibrinopeptide A; fibrin II (clear), fibrin which lacks both fibrinopeptide A and B.

Appellant submits that Table 1 of VAILHE et al. teaches that all the mentioned cells can be used for in vitro angiogenesis and vasculogenesis. More precisely, Table 1 of VAILHE et al. teaches that BAEC (Bovine Aortic Endothelial Cells), from foetus or calf, are spontaneously able to induce morphogenesis when they are seeded on a plate without a cellular matrix component. On the contrary, HUVEC (Human Umbilical Vein Endothelial Cells) and BREC (Bovine Retinal Endothelial Cells) cells are spontaneously able to induce morphogenesis when they are seeded on a plate coated with fibrin. Appellant concludes that VAILHE et al. teach that BREC cells and HUVEC cells are the closest art, in terms of angiogenic potentialities, compared to FBAEC. Consequently, the skilled person would be motivated from the teachings of VAILHE et al. to replace HUVEC cells taught in the method by SAITO et al., by BREC cells instead of FBAEC cells.

This is not found persuasive for following reasons:

Contrary to Appellant's arguments, a prior art reference may be considered to teach away when

"a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

Here in contrast to appellant's assertions of teaching away by the prior art because the Concina et al reference indicates successful means and methods for obtaining FBAEC cells as an in vitro model of endothelial cell proliferation and reendothelialization in a medium containing a supplement of oestradiol which was able to induce VEGF synthesis in a dose-dependent fashion; there is no discouragement nor skepticism in the prior art for using FBAEC as the antigen. In addition, both Concina et al and Vailhe et al references indicate that FBAEC cells as an in vitro model of angiogenesis and vasculogenesis (see table 1, row 4 of Vailhe and Fig. 3 of Concina et al), Concina et al show FBAEC cells to be sensitive to E2 stimulation in a dose-dependent manner; there is no discouragement nor skepticism in the prior art for the use of FBAEC cells in terms of angiogenic potentialities, particularly in light of the prior art teachings to provide the number of cells as a model for angiogenesis and vasculogenesis including FBAEC. Furthermore, Concina et al teach that endothelial cells in particular appear to be a target for estradiol 17β (E2) because endothelial cells express the estrogen receptor (see page 202, under Introduction). Given that all endothelial cells express the estrogen receptor, then all endothelial cells listed in Table 1 of Vailhe et al would respond to oestradiol and induce VEGF synthesis and form capillary-like structure (angiogenesis and vasculogenesis).

On the top of page 9 of the brief, Appellant submits that at the time that the invention was made, one of skill in the art would have known that bovine retinal endothelial cells (BREC) cells stimulation by oestradiol induces VEGF gene expression in a dose dependant manner, and also induces VEGF protein expression. This is evidenced respectively in Figure 4 and Figure 5 of SUZUMA et al. (Investigative Ophtalmology & Visual Science, 1999, Vol 40, n. 9, pp: 2122-2129). Appellant concluded that from the teachings of SUZUMA et al. and the teachings of VAILHE et al., the skilled person would be motivated to use the BREC of SUZUMA et al. instead of the FBAEC of CONCINA et al. to produce antibodies directed against tumor vasculature as disclosed in SAITO et al. Appellant argues that when substituting SAITO et al.

cells by either SUZUMA et al. cells or CONCINA et al. cells, the skilled person would be led in direction divergent from the path that was taken by the appellant.

This is not found persuasive for following reasons:
The claims are drawn to the use of endothelial cells removed from an aorta not from a retina. The use of the bovine retinal endothelial cells (BREC) is immaterial to the claimed process for preparing a monoclonal antibody. The rejection was made over Concina et al reference but not over Suzuma et al reference because Concina et al use aortic endothelial cells which makes reference the closest prior art to the claimed invention. Also, Vailhe et al teaches that bovine aortic endothelial cells-BAEC (fetal and calf) can be used in *in vitro* models of angiogenesis and vasculogenesis (see table 1, row 4), Suzuma et al uses the calf BREC to study the effect of oestradiol on the induction of VEGF gene expression. Concina et al use the fetal BAEC to also study the effect of E2 on VEGF content in conditioned medium of FBAEC. According to Vailhe both fetal and calf BAEC can be used for in vitro models of angiogenesis and vasculogenesis, thus fetal and calf BAEC and BREC are interchangeable as an in vitro model for angiogenesis and vasculogenesis. Indeed, Appellant's own specification on page 6, lines 12-14 and claim 32, filed 02/27/2006 discloses that the endothelial cells characterized in that these are endothelial cells of vessels, in particular endothelial cells of the aorta, adrenal cortex, skin, cerebrum, retina, veins or umbilical cord artery. Also, Appellants cannot represent to the public that their endothelial cells can be derived from aorta, adrenal cortex, skin, cerebrum, retina, veins or umbilical cord artery, while at the same time discounting the relevance of these endothelial cells to the obviousness of their claim.

On the bottom of page 10 of the brief, Appellant submits that claim 36 of the present invention sets forth that "said endothelial cells having an angiogenic phenotype being obtained by culturing endothelial cells removed from an aorta in a medium consisting essentially of oestradiol and VEGF, said endothelial cells with an angiogenic phenotype being such that… their expression of VEGFR-2 is increased 4- fold in comparison with cells with a non-angiogenic phenotype" (emphasis added by Appellant). This 4-fold increase in expression represents a result that is unexpected in light of the applied art. This result is thus analogous to the case where a many-fold

improvement of activity over the prior art held sufficient to rebut *prima facie* obviousness based on close structural similarity. *In re Wiechert*, 370 F.2d 927, 152 USPQ 247 (CCPA 1967). Here, there is no structural similarity but rather a restriction to two factors: oestradiol and VEGF. SUZUMA et al. teach that oestradiol treated BREC cells are able to express VEGF growth factor, but also VEGFR-2 receptor. Moreover, at an oestradiol dosage of 10^{-8} M (i.e., 10 nM), the level of VEGFR-2 mRNA is increased 2.4 ± 0.3 times compared to untreated BREC cells. This increase corresponds to the maximal increase at this dosage (see page 2126, second column, first paragraph). In contrast to the teachings of SUZUMA et al., CONCINA et al. never mention that the oestradiol stimulation enhances VEGFR-2 gene expression, or the level of the aforesaid enhancement, if it exists. Without such information, one of skill in the art would be led to prefer SUZUMA et al.'s cells instead of CONCINA et al.'s cells. Consequently, at the time the invention was made, one of ordinary skill, having a knowledge of all the prior art of relevance, would be seek to provide a method for producing antibodies specifically interacting with endothelial cells having angiogenic phenotype, by using SUZUMA et al. BREC cells stimulated with oestradiol, and secreting VEGF. However, since one of the main features of the endothelial cells having an angiogenic phenotype used in this method is missing, the skilled person would be led in a direction divergent from the path that was taken by the applicant. Appellant submits that since the cells used for the implementation of the method of SAITO et al. are different, the resulting monoclonal antibodies obtained by the method of SAITO et al. will be consequently different.

This is not found persuasive for following reasons:
However, while the expression of VEGFR-2 is increased 4-fold is material claim limitation, the statement of the intended result of supplementing oestradiol and VEGF does change VEGFR-2 expression or otherwise limit the claim. However, a person having ordinary skill in the art would have found it obvious to determine the optimum values of result-effective variables known in the art. The claimed angiogenic phenotype “expression of VEGFR-2 is increased 4-fold in comparison with cells with a non-angiogenic phenotype" of the FBAEC does not result in a manipulative difference in the method steps of the claims. The recitation of “expression of VEGFR-2 is increased 4-fold in comparison with cells with a non-angiogenic phenotype” is a

statement of the intended results of the treatment of the FBAEC with oestradiol and VEGF; the combined reference teaching arrived to the use of oestradiol treatment which induces the release of VEGF. Appellant's arguments with respect to Suzuma and Vailhe are irrelevant to the rejection of record because the rejection was not made over Suzuma or Vailhe but rather was made over Concina et al.

On the bottom of page 12 of the brief, Appellant submits that the inventiveness of the present invention resides, in part, in that for the first time endothelial cells with angiogenic phenotypes that have been stimulated by only two exogenous growth factor and hormones: VEGF and oestradiol (emphasis added by Appellant). This particular growth factor and hormone stimulation confer to the cells specific new and inventive characteristics, allowing to obtain a new and inventive method for producing antibodies specifically directed against tumor vasculature. Appellant submits that if the skilled person has been motivated, for any reason, to combine the teachings of SAITO et al. and the teachings of CONCINA et al., the skilled artisan would obtain a method for producing monoclonal antibodies directed against endothelial cells having angiogenic phenotype, but the endothelial cells having angiogenic phenotype obtained would never have an expression of VEGFR-2 increased 4-fold in comparison with cells with a non-angiogenic phenotype. Appellant submits that one of the aims of the present invention is the importance of the exogenous addition of VEGF in the cell culture medium, which has a significantly higher efficacy than the VEGF secreted in response to oestradiol treatment (emphasis added by Appellant).

This is not found persuasive for following reasons:

Concina's et al initial medium does not contain oestradiol and VEGF, Concina et al treatment of FBAEC with E2 was able to induce VEGF synthesis in a dose-dependent fashion (see Fig. 3). Accordingly, the media was supplemented with both oestradiol and VEGF because the initial medium does not contain either the oestradiol or the VEGF. After FBAEC treatment with E2 the medium contain both oestradiol and VEGF. Therefore, the medium was supplemented with both oestradiol and VEGF. There is no requirement that the VEGF should be added exogenously.

Claim 36 recites "culturing endothelial cells removed from an aorta in a medium containing a supplement consisting essentially of oestradiol and VEGF"; Concina et al treatment with E2 was able to induce VEGF synthesis in a dose-dependent fashion (see Fig. 3). Thus, the term "a medium containing a supplement" does not mean that the supplement is exogenous. Furthermore, given the teachings of Concina et al that local delivery of VEGF accelerates the reendothelialization and a pharmacological dose of E2 also promotes reendothelialization (see page 203, left col. 1st full ¶), and that the mitogenic effect of E2 on *in vitro* endothelial cell proliferation and on *in vivo* reendothelialization are both dependent on VEGF (see title), it would have been obvious to one skilled in the art at the time the invention was made to exogenously supplement the medium with oestradiol and VEGF to induce cell proliferation and reendothelialization. It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06. The claimed angiogenic phenotype of an expression of VEGFR-2 increased 4 fold in comparison with cells with a non-angiogenic phenotype is considered an expected result of the treatment of FBAEC cells with E2 which induce VEGF synthesis in a dose-dependent fashion.

7.1.1 Rebuttal to Office's Arguments [Rebuttal to the Final Office Action]

On page 13 of the brief, under section 7.1.1, Appellant argues with respect to teaching away by the prior art issue that one of skill in the art would also be cognizant of the teachings of Figure 4 and Figure 5 of SUZUMA et al., discussed above, and be led to use BREC of SUZUMA et al. instead of FBAEC of CONCINA et al. to produce antibodies directed against tumor vasculature as disclosed in SAITO et al.

This is not found persuasive for following reasons:

As Appellant points out Suzuma et al concerns with bovine retinal endothelial cells, BREC, but the claimed process uses aortic endothelial cells. Concina et al uses aortic endothelial cells,

therefore, Concina et al teachings are closer art to the claimed invention. The BREC of Suzuma et al reference is not claimed, therefore, Suzuma et al teachings are irrelevant to the claimed invention. Moreover, the teachings of Suzuma et al reference are not part of the rejection of record. Accordingly, Concina et al is the closest art to appellant claimed invention and is the art used in the rejection of record.

On page 15 of the brief, Appellant argues with respect the interchangeability of the endothelial cells based on the formation of angiogenesis and vasculogenesis that these complex biochemistries are extremely unpredictable, and that there is no basis for the assumption that the foetal and calf BAEC are interchangeable in regards to the effect of E2 on VEGF content in a conditioned medium of FBAEC.

This is not found persuasive because Concina et al teaches that endothelial cells in particular appear to be a target for estradiol 17β (E2) because endothelial cells express the estrogen receptor (see page 202, under Introduction). Given that the endothelial cells express the estrogen receptor, one skilled in art would predict that the endothelial cells to be responsive to the E2 in the same manner as the FBAEC. As is evidenced by Suzuma et al that the BREC is responsive to the E2 by receptor-mediated pathway and that E2 may augment the VEGF-dependent angiogenesis partly through the upregulation of VEGFR2 (see abstract).

On the bottom of page 15 of the brief, Appellant argues that "expression of VEGFR-2 is increased 4-fold in comparison" is a limitation due patentable weight, and not a result of optimization or intended result. That is, this term can be considered a functional limitation that is due patentable weight. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971). A functional limitation is often used in association with an element, ingredient, or step of a process to define a particular capability or purpose that is served by the recited element, ingredient or step. *Innova/Pure Water Inc. v. Safari Water Filtration Sys. Inc.*, 381 F.3d iiii, 1117-20, 72 USPQ2d i001, 1006-08 (Fed. Cir. 2004). Moreover, the 4-fold increase, even if claimed, is clearly an unexpected result in a very complicated field in which routine optimization is rare. The 4-fold increase is clearly set forth in the "Results" at pages 26 and 27 of the specification.

Rebuttal evidence and arguments can be presented in the specification, *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 Fed. Cir. 1995), by counsel, In re Chu, 66 F.3d 292, 299, 36 USPQ2d 1089, 1094-95 (Fed. Cir. 1995). Examiners must consider comparative data in the specification which is intended to illustrate the claimed invention in reaching a conclusion with regard to the obviousness of the claims. In re Margolis, 785 F.2d 1029, 228 USPQ 940 (Fed. Cir. 1986).

This is not found persuasive because Appellant's reliance on unexpected results do not overcome clear and convincing evidence of obviousness. Also see *Richardson-Vicks Inc. v. Upjohn Co.*, 44 USPQ2d 1181 (CAFC 1997). The issue is whether the properties differ to such an extent that the difference is really unexpected. In the instant case, Suzuma et al explicitly discloses the same unexpected results as presented in the specification. Suzuma et al teach that a significant increase in VEGFR2 in BRECs was observed 6 hours after treatment with E2 (see page 2128, 1st col., 2nd full ¶). Accordingly, the claimed unexpected results with oestradiol and VEGF treatment compared to absence of treatment would be expected based on the Suzuma teachings. Accordingly, there is nothing unexpected about Appellant's results and showings. When the ingredients are associated in an obvious manner set forth in the claims, they do not co-act with each other in any new or unexpected way and define nothing patentable over the prior art. Therefore, one of ordinary skill in the art at the time of the invention was made would expect the oestradiol and VEGF of the invention to possess the expected significant increase in VEGFR2 after treatment with oestradiol and VEGF. When considering obviousness of a combination of known elements, the operative question is thus "***whether the improvement is more than the predictable use of prior art elements according to their established functions***." *KSR at 418* (emphasis added). In the instant case, the inventor merely used routine research methods to prove what was already believed to be the case.

On the top of page 17 of the brief, Appellant argues that with SUZUMA and VAILHE are irrelevant to the rejection of record that SUZUMA et al. and VAILHE et al. were provided by the Appellant as evidence of the state of the art, to further demonstrate that the conventional art

typified by CONCINA et al. would not lead one of skill (at the time the invention was made) to combine the references in a fashion to produce a claimed embodiment of the present invention. Moreover, SUZUMA et al. and VAILHE et al. have been submitted for consideration in the IDS of September 21, 2009. Once the applicant has presented rebuttal evidence, Office personnel should reconsider any initial obviousness determination in view of the entire record. See, e.g., *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984); *In re Eli Lilly & Co.*, 90 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). Appellant concluded that a person with ordinary skill would never obtain the present invention, as claimed, from knowledge of the teachings of SAITO et al. and the teaching of CONCINA et al. in light of the art of record. A *prima facie* case of unpatentability has thus not been made. Moreover, any unpatentability that could be alleged is rebutted by the unexpected results.

This is not found persuasive because it remains the Examiner's position that Suzuma et al and Vailhe et al teachings are irrelevant to the rejection of record because the rejection of record was not made over Suzuma et al and Vailhe et al but rather over, Saito et al in view of Concina et al. The combined reference teachings arrived to the claimed invention. Even viewed as "rebuttal evidence", Suzuma et al and Vailhe et al teachings are not persuasive because all endothelial cells appear to be a target for estradiol 17β (E2) because endothelial cells express the estrogen receptor (Concina et al, page 202, under Introduction). Accordingly, these endothelial cells would be interchangeable in the claimed process. It would have been obvious to one skilled in the art at the time the invention was made to immunize the E2-treated FBAEC which induce VEGF synthesis taught by Concina et al in a method of producing monoclonal antibodies reactive with tumor vasculature taught by Saito et al. Given that local delivery of VEGF accelerates the reendothelialization and a pharmacological dose of E2 also promotes reendothelialization, it would have been obvious to one skilled in the art at the time the invention was made to exogenously supplement the medium with oestradiol and VEGF to induce cell proliferation and reendothelialization. It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; the idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA

1980. See MPEP 2144.06. Those of skill in the art would have had reason to use the FBAEC taught by Concina et al as a substitute for the immunization of mice taught in Saito et al because, like the HUEVC taught in Saito et al, FBAEC cells treated with Oestradiol and VEGF have angiogenic phenotype.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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